2004

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T Realini

The Uniocular Drug Trial and Second-Eye Response to Glaucoma Medications

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Purpose: To determine if the intraocular pressure (IOP) reduction observed in a uniocular trial correlates with the IOP reduction seen in the fellow eye when the same medication is then administered to the second eye of patients with glaucoma.

Study Design: Observational case series.

Participants: Fifty-two patients with bilateral glaucoma.

Methods: Glaucoma patients underwent uniocular trials of various glaucoma medications, then subsequently received the same drug in the fellow eye. The IOP reduction observed in the first eye was compared with that observed in the second eye to determine correlation.

Main Outcome Measure: Intraocular pressure reduction in fellow-eye pairs.

Results: Intraocular pressure dropped a mean of 5.7±3.8 mmHg (mean ± standard deviation) in the first eye after a uniocular trial, and 2.8±3.3 mmHg in the second eye after bilateral use. Regression analysis demonstrated a poor correlation between first-eye and second-eye response to the same medication ($r^2 = 0.0174$). To minimize possible contralateral IOP effects of first-eye therapy, a subset of 26 patients treated with latanoprost (which has little if any contralateral IOP effect, due to rapid systemic metabolism) was studied, with no improvement in correlation ($r^2 = -0.0023$).

Conclusion: Uniocular trials of glaucoma medications do not adequately predict second-eye IOP responses to the same medications. If both eyes of a glaucoma patient require IOP reduction, one should not assume that magnitudes of response will be equal in both eyes. The effect of a given medicine must be assessed independently for each eye. *Ophthalmology 2004;111:421–426 © 2004 by the American Academy of Ophthalmology.*

The uniocular drug trial, also called the monocular drug trial, is a valued tool in glaucoma management. The textbooks of Shields[1]; Becker-Shaffer[2]; and Ritch, Shields, and Krupin[3] all recommend employing the uniocular drug trial to assess individual patient responses to glaucoma medications. At least one major clinical trial has also required uniocular trials in its protocol.[4]

In a uniocular drug trial, a patient receives a given medication in one eye only. After a treatment period long enough to achieve a steady-state effect, the reduction from baseline in intraocular pressure (IOP) in the treated eye is assessed. If an acceptable IOP reduction has been achieved in the first eye, the drug is deemed effective in the patient, and both eyes are subsequently treated with the drug. The IOP reduction in the second eye to receive the drug is assumed to be approximately equivalent to the first-eye response, and is not typically assessed after bilateral therapy is initiated.

This study was undertaken to determine if the IOP reduction observed in a uniocular trial correlates with the IOP reduction seen in the fellow eye when the same medication is then administered to the second eye of patients with glaucoma.

Materials and Methods

This study was approved by the Human Research Advisory Committee at the University of Arkansas for Medical Sciences and the Institutional Review Board at the University of Medicine and Dentistry of New Jersey.

Medical records of glaucoma patients seen in university-based glaucoma specialty practices were reviewed. Inclusion criteria for eligible patients included age 18 to 100 years; diagnosis of glaucoma in both eyes; and progressive addition of a topical antiglaucoma medication, first in one eye, then in the second eye, with IOP determination before and after use of the medication in each eye.

Once identified, data collected from the charts included demographic information, type of glaucoma, ocular medications, and pertinent IOP readings from the ocular examinations at which the uniocular trial was commenced, when the uniocular trial was assessed and second-eye treatment initiated, and when the patient

Originally received: March 26, 2003.
Accepted: August 14, 2003. Manuscript no. 230173.

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Presented in part at: Association for Research in Vision and Ophthalmology meeting, May, 2002; Ft. Lauderdale.

Supported in part by unrestricted grants from Research to Prevent Blindness, Inc., New York; the Pat and Willard Walker Eye Research Center, Little Rock; and the Lions Eye Research Foundation of New Jersey.

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ISSN 0161-6420/04/$–see front matter
doi:10.1016/j.ophtha.2003.08.022

Table 1. Flow Diagram for Data Collection Sequence

A. Sequence for 43 patients	
Visit A	First-eye baseline IOP established
	First-eye treatment started
Visit B	First-eye IOP change determined
	Second-eye baseline determined
	Second-eye treatment started
Visit C	Second-eye IOP change determined
B. Sequence for 9 patients	
Visit A	First-eye baseline IOP established
	First-eye treatment started
Visit B	First-eye IOP change determined
Visit C	Second-eye baseline determined
	Second-eye treatment started
Visit D	Second-eye IOP change determined

IOP = intraocular pressure.

next returned using the medication in both eyes. In most cases, these were 3 consecutive visits. In 9 cases, the medication was not added to the second eye on the uniocular trial assessment visit, but was added at a later visit; in these cases, the first-eye uniocular IOP effect was assessed at the 2 consecutive visits beginning with addition of medication to the first eye, and the second-eye effect was assessed at the 2 consecutive visits beginning with addition of medication to the second eye (Table 1).

Although specific time frame data between visits were not collected, in general we allow 4 to 6 weeks between the initiation of treatment and the assessment of treatment effect in the uniocular trial; once the medication is added to the fellow eye, the IOP reduction in the fellow eye is typically assessed at the next scheduled visit, 3 to 4 months later.

Data analysis included linear regression analysis using the Pearson correlation coefficient, *r*. *P* values of ≤ 0.05 were considered statistically significant. Analysis was performed on the entire cohort. Subset analysis of patients treated with latanoprost was performed to eliminate the potential contralateral crossover effect (latanoprost is unlikely to have a contralateral IOP-lowering effect[5]). A separate subset analysis of patients with primary open-angle glaucoma (POAG) was performed to determine if the type of glaucoma affected symmetry of IOP responses between fellow eyes of glaucoma patients. An additional subset analysis of patients with no history of glaucoma surgery (laser or incisional) was undertaken to exclude prior glaucoma surgery as a source of noncorrelation.

Results

Fifty-two eligible charts were identified and included in this analysis. Overall, 73.1% were female, 71.2% were white, and the mean age (± standard deviation [SD]) was 66.0±14.0 years. Table 2 shows the medications used in the uniocular trials analyzed in this report.

Does the First-Eye Response Predict the Second-Eye Response?

Among the 52 first-treated eyes undergoing uniocular trials with various medications, mean IOP (± SD) dropped from a pretrial baseline of 22.4 (±5.2) mmHg to 16.7 (±4.3) mmHg, a 5.7-mmHg (25.4%) reduction. When the same medication was then added to the second eye of each patient, mean IOP in the second eye dropped from pretreatment baseline of 19.7 (±4.2) mmHg to 16.9 (±3.7) mmHg, a 2.8-mmHg (14.2%) reduction. The Pearson correlation coefficient, *r*, for the correlation between IOP reduction in the first and second eyes was 0.13 ($r^2 = 0.017$, $P = 0.352$), demonstrating essentially no correlation between the magnitude of IOP responses of fellow eyes (Fig 1).

Table 2. Patient Characteristics and Drugs Used in Uniocular Trials

Diagnosis [n (%)]	
Primary open-angle glaucoma	31 (59.6)
Glaucoma suspect	12 (23.1)
Chronic angle-closure glaucoma	5 (9.6)
Normal tension glaucoma	3 (5.8)
Pigmentary glaucoma	1 (1.9)
Gender [n (%)]	
Female	38 (73.1)
Male	14 (26.9)
Race [n (%)]	
White	37 (71.1)
Black	13 (25)
Other	2 (3.8)
Median age (yrs)	67
Medication class used in trial [n (%)]	
Prostaglandin analogue	27 (51.9)
β-blocker	14 (26.9)
Carbonic anhydrase inhibitor	5 (9.6)
α-Adrenergic agonist	4 (7.7)
β-blocker–carbonic anhydrase inhibitor fixed combination	2 (3.8)
Enrollment site [n (%)]	
Little Rock	36 (69.2)
Newark	16 (30.8)

Given that the average IOP in the second-treated eye before treatment was lower than that of the first-treated eye before treatment, it was possible that a smaller absolute IOP change might represent an equivalent percent change in IOP. We repeated the analysis using the percent IOP change from baseline, and found that first-treated eyes experienced a mean individual IOP reduction of 25%, compared with a 13% mean individual IOP reduction in second-treated eyes. The Pearson correlation coefficient and its square for the correlation between percent IOP reduction in fellow eyes were 0.17 and 0.03, respectively ($P = 0.22$).

Does a Contralateral Crossover Effect Affect Predictive Ability of the Uniocular Trial?

We separately analyzed a subset of 26 patients treated with latanoprost, which is unlikely to have a contralateral IOP-lowering effect.[5] Among the 26 first-treated eyes undergoing uniocular trials with latanoprost, mean IOP (± SD) dropped from a pretrial baseline of 20.4 (±4.0) mmHg to 15.2 (±4.2) mmHg, a 5.2-mmHg (25.5%) reduction. When latanoprost was then added to the second eye of each patient, mean IOP in the second eye dropped from a pretreatment baseline of 18.6 (±3.4) mmHg to 15.4 (±2.8) mmHg, a 3.2-mmHg (17.2%) reduction. Comparing IOP reduction in first and second eyes treated with latanoprost, the Pearson correlation coefficient was 0.16 ($r^2 = 0.024$, $P = 0.449$), again demonstrating essentially no correlation between IOP responses of fellow eyes treated with latanoprost (Fig 2).

Does the Type of Glaucoma Affect Predictive Ability of the Uniocular Trial?

A subset of 31 patients with POAG was analyzed separately. The Pearson correlation coefficient, *r*, for the correlation between IOP

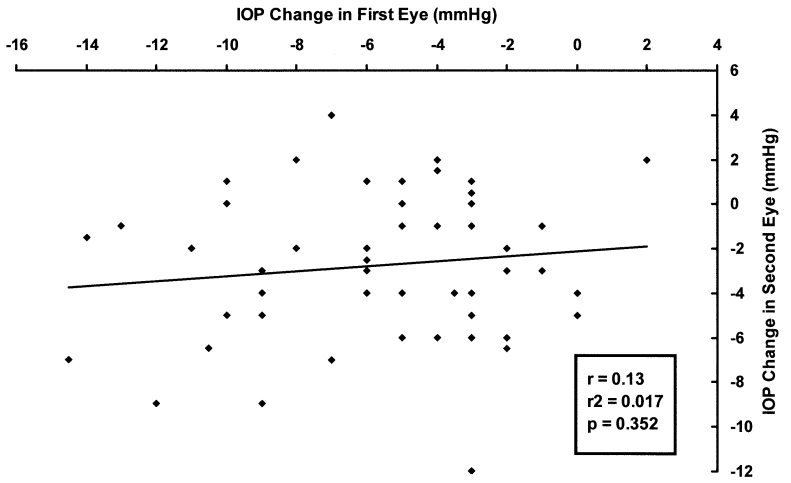

Figure 1. Correlation of intraocular pressure (IOP) reduction among fellow eyes (n = 52).

reduction in the first and second eyes was 0.13 ($r^2 = 0.017$, $P = 0.483$), demonstrating essentially no correlation between IOP responses of fellow eyes.

Does a History of Glaucoma Surgery Affect Predictive Ability of the Uniocular Trial?

Six patients in the cohort had undergone unilateral or bilateral laser trabeculoplasty or trabeculectomy before the uniocular trial. The subset of 46 patients with no history of laser or incisional glaucoma surgery was analyzed separately. The Pearson correlation coefficient, *r*, for the correlation between IOP reduction in the first and second eyes was 0.13 ($r^2 = 0.017$, $P = 0.392$), demonstrating essentially no correlation between IOP responses of fellow eyes.

Discussion

The uniocular drug trial has long been used to determine individual responsiveness to glaucoma medications. Despite its popularity, the assumptions upon which the uniocular trial is based have been incompletely characterized. In the most common interpretation of the uniocular trial, the therapeutic response of the tested drug is determined by subtracting the IOP change in the untreated eye from the IOP change in the treated eye. The rationale is that, had both eyes remained untreated, the IOP changes would have been symmetric in fellow eyes, and that the untreated eye provides an internal control that allows for assessment of nontherapeutic IOP changes.

This method of interpreting the uniocular trial is multiply flawed. First, it is well known that some drugs—particularly β-blockers—exert a contralateral IOP reduction, most likely due to systemic absorption and delivery to the fellow eye.[4] Thus, simply subtracting the untreated-eye IOP change from the treated-eye IOP change will underestimate the therapeutic effect of the drug. Second, and far more important, the existing data demonstrate that IOP behavior in fellow eyes is not symmetric. In a study performed over 4 decades ago, Katavisto[6] demonstrated that diurnal IOP curves for fellow-eyes pairs are often dissimilar in shape,

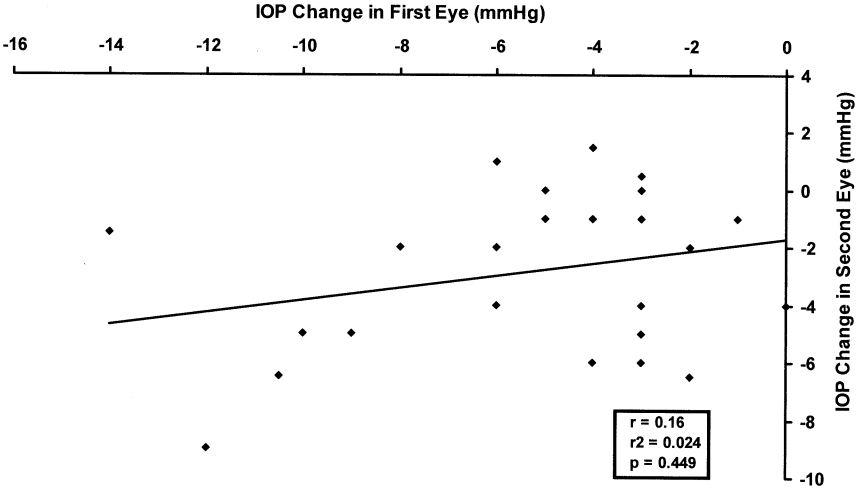

Figure 2. Correlation of intraocular pressure (IOP) reduction between fellow eyes treated with latanoprost (n = 26).

with IOP maxima and minima occurring at different times of day for each eye. A similar study by Wilensky and colleagues[7] 3 decades later demonstrated the same phenomenon: 33% of ocular hypertension patients and 36% of POAG patients exhibited asymmetry of diurnal curve shapes between fellow eyes. More recently, a study by Realini and coworkers[8] revealed that spontaneous asymmetric IOP changes between fellow eyes of ≥3 mmHg are extremely common, occurring in over 63% of glaucoma patients on stable medication regimens.

Using the untreated fellow eye as a control to assess therapeutic IOP responses can lead to an interpretive quagmire. Consider the following clinical example: a patient with untreated IOPs of 22 mmHg in both eyes begins treatment in the right eye, and 1 month later, IOPs are 24 mmHg in the right eye and 30 mmHg in the left. Using the untreated left eye as a control, we determine that the medication lowered IOP 6 mmHg (treated eye response minus untreated eye response gives $+2 - +8 = -6$), despite the indisputable fact that the IOP in the treated eye is higher on medication than it was before treatment! Does one deem the medication successful and begin treatment bilaterally? Obviously, some do: a careful look at Figure 1 will reveal 1 patient whose first-eye IOP change was +2 mmHg, 2 more patients with no change in IOP after first-eye treatment, and 6 more patients whose IOP was reduced only 1 or 2 mmHg; in all of these patients, the uniocular trial was deemed a success, and treatment was begun in the second eye.

We are not confident that fellow eyes can serve as each others' controls. This is not to say that IOP is not similar in fellow-eye pairs. Indeed, very likely it is—*on average*. Over time, the average IOP is likely to be very similar in fellow-eye pairs. But to believe that the IOP in fellow eyes is identical or nearly so at every instant is not supported and, in fact, is disproved by the existing literature.

For this reason, our analysis of the uniocular trial in this study was undertaken using only the information collected from the treated eye, with no correction for the IOP change in the untreated fellow eye. Our data show surprisingly but convincingly that the uniocular drug trial does not predict second-eye IOP reductions after treatment with the same medication.

Why might this be? In the uniocular trial flowchart (Table 1), the IOP change observed between visits A and B is considered to be the therapeutic change resulting from treatment with an IOP-lowering drug. But in fact, the IOP difference between time points A and B represents both a therapeutic component and a nontherapeutic, spontaneous component of IOP change. Intraocular pressure in glaucomatous eyes does not remain constant over time; spontaneous changes in IOP in glaucomatous eyes are well established.[6–8] Similarly, the IOP difference between time points B and C represents both therapeutic and spontaneous IOP changes for the second eye treated, and our inability to demonstrate correlation between first-eye and second-eye IOP reductions to glaucoma medications might be due to:

- asymmetry of the therapeutic component of IOP change in fellow eyes;
- variability of the spontaneous (nontherapeutic) component of IOP change in fellow eyes;
- regression to the mean.

Asymmetry of the Therapeutic Component

We wonder if intereye response differences are related to asymmetric trabecular meshwork damage and asymmetric outflow impairment between fellow glaucomatous eyes. In simplest terms, IOP is determined by outflow resistance in the trabecular meshwork. Outflow resistance is increased in eyes with glaucoma. In that glaucoma is uncommonly perfectly symmetric in fellow eyes, it is not unexpected that IOP should behave asymmetrically as well. Indeed, as noted above, several studies have demonstrated asymmetry of various aspects of IOP. Wilensky et al[7] and Katavisto[6] described asymmetry in the shapes of diurnal IOP curves in fellow eyes of glaucoma patients, and we have reported asymmetric IOP fluctuations in fellow eyes of glaucoma patients.[8]

It is less obvious, however, how potentially asymmetric outflow might be related to asymmetric responses to IOP-lowering medications. We might expect medications that act to enhance trabecular outflow to have asymmetric effects in fellow eyes if asymmetric trabecular outflow is present. We are less certain why medications that act to reduce aqueous production or to enhance nontrabecular outflow would have asymmetric effects even in eyes with asymmetric trabecular outflow.

Variability of the Spontaneous (Nontherapeutic) Component

Intraocular pressure is a dynamic function and fluctuates in both normal subjects and glaucoma patients, generally more so in the latter group. The list of variables that can cause nontherapeutic changes in IOP (i.e., independent of treatment with glaucoma medications) is long and diverse, and can include body position, breath holding, and fluid consumption, among countless others. In the present study, the effect of a given medication in one eye over one time frame is compared with the effect of the same medication in the fellow eye over a different time frame. A key problem with this study design and, indeed, with the concept of the uniocular trial is that different time frames are subject to different IOP-changing variables. For instance, a patient who wore a tight necktie at visit A but no necktie at visits B and C will have different IOP-affecting variables at play in the first-eye and second-eye analysis time frames. In this hypothetical scenario, the therapeutic IOP response to a given glaucoma medication might have been equivalent in the eyes, but nontherapeutic IOP changes would potentially confound data analysis and prevent observation of correlation.

Regression to the Mean

In this retrospective study, uniocular trials were initiated when the IOP was higher than deemed tolerable. Accordingly, some of the IOP reduction observed after treatment might be attributable to regression to the mean.

Regression to the mean occurs when a reduction in IOP occurs spontaneously rather than therapeutically, and in a study designed to determine the IOP-lowering efficacy of a medication, regression to the mean can improve a drug's apparent performance. *Regression to the mean* is a statistical term and not a physical process. By this, we mean that the term describes an observed change in IOP but does not offer an explanation for that change. In fact, regression to the mean is a catch-all phrase that describes what we choose to define more causally as the spontaneous (nontherapeutic) component of IOP change.

Our study's goal was to demonstrate a *difference* in IOP responses of fellow eyes to the same medication. We found that a difference exists. Because our study was retrospective, each eye underwent IOP reduction based on a threshold IOP level deemed too high by the treating clinician; it is in this setting that regression to the mean manifests, and in our study, regression to the mean should have occurred in both eyes, which might have increased correlation. Labeling the difference in fellow-eye responses as a regression to the mean does not make the difference go away, and more importantly, labeling it thus offers no explanation regarding the physiologic basis for the difference.

Does a Contralateral Crossover Effect Affect Predictive Ability of the Uniocular Trial?

Zimmerman and Kaufman[9] proposed that timolol applied in one eye could lower IOP in the fellow eye via systemic absorption and delivery. More recently, the contralateral crossover effect of unilaterally administered β-blockers was quantified in a substudy analysis of the Ocular Hypertension Treatment Study.[4] In this study, mean IOP dropped almost 6 mmHg (22%) in the treated eyes, and 1.5 mmHg (5.8%) in the untreated contralateral eyes.

In our study, we observed a lower baseline IOP in the second eye (19.7 mmHg) than in the first eye to be treated (22.4 mmHg, a 2.5-mmHg difference) and a smaller drop in IOP in second eyes. As the second-eye baseline was obtained after treating the first eye, we suspected a contralateral crossover effect from the medication instilled in the first eye.

We investigated this possible source of error in 2 ways. First, we calculated the IOP difference between fellow eyes at the preuniocular trial baseline (before either eye received the uniocular trial drug) and found that the mean IOPs in the first eye (22.4 mmHg) and second eye (20.4 mmHg) differed by 2 mmHg even before undergoing the uniocular trial. This difference likely reflects an artifact of the retrospective nature of the study: the eye with the higher pressure was more likely to be chosen as the first-treated eye. Because the difference in IOPs between eyes was present even before the uniocular trial, we felt it was unlikely to represent a therapeutic contralateral crossover effect. To be more certain, we separately analyzed the 26 patients treated with latanoprost to see if the correlation improved when the possibility of a significant crossover effect was eliminated. (In at least one clinical trial, no crossover effect was seen with latanoprost.[5]) In this analysis, the correlation between first-eye and second-eye IOP reductions to latanoprost was no better than the correlation for the entire 52-patient cohort. Thus, we feel confident that the differences in first- and second-eye IOP responses were not attributable to contralateral crossover effects in this study.

Does the Type of Glaucoma Affect Predictive Ability of the Uniocular Trial?

As previously discussed, it seems intuitive that in hypothetical symmetric glaucoma we might expect symmetric responses to a given medication. In hypothetical asymmetric glaucoma (worse in one eye than in the other), the converse is not necessarily true: even if the trabecular outflow is asymmetrically impaired in fellow eyes, would we really expect—for instance—a medication that works to enhance uveoscleral outflow to work differently in these fellow eyes?

To explore this issue a bit further, we separately analyzed the data from patients with POAG and from patients with non-POAG. Symmetric trabecular outflow impairment of fellow eyes is probably more likely in POAG patients than in non-POAG patients, and we hoped to demonstrate better correlation between first- and second-eye IOP responses in POAG eyes. Alas, although both analyses showed abysmal correlation, the non-POAG analysis had marginally *better* correlation than the POAG eyes (data not shown)!

Does a History of Glaucoma Surgery Affect Predictive Ability of the Uniocular Trial?

Along the same lines as above, we considered that a patient with a functioning filtering bleb in one eye might exhibit asymmetric therapeutic responses, and repeated the analysis excluding the 6 patients with a history of laser or incisional glaucoma surgery. Even with these potential confounders removed, the remaining glaucoma surgery–naïve patients exhibited no correlation in unilateral and second-eye treatment responses.

This retrospective study is subject to all the limitations and artifacts known to affect such endeavors. Despite the limitations, our findings are not merely of marginal statistical significance. No matter how we attempted to clean the data to minimize artifacts, there simply was no correlation to be found between the uniocular trial results and the second-eye IOP response.

We are underway with additional studies to further elucidate these preliminary findings, and we suggest 2 consequences of our current findings. The first is that the uniocular trial is likely to be unhelpful and unnecessary in glaucoma management. The purpose of the uniocular trial is to determine if a given drug works for a given patient. This is based on the assumption that fluctuation in IOP tends to be similar in both eyes. This is not true. We also have assumed that if one eye responds well to a medication, the other will as well. Our data do not support that assumption. Therefore, none of the assumptions underlying the one-eye trial are supported by our retrospective studies. Instead, we need a trial that determines if a given drug works for a given eye, and the same test must be performed on both eyes of a

two-eyed patient. The simplest solution is to begin treatment in both eyes simultaneously and assess each eye separately in terms of IOP response. We cannot generalize the IOP response to treatment observed in one eye to the fellow eye.

The second consequence is broader: if fellow eyes have independent IOP responses to a given drug, we may be able to reduce the number of subjects enrolled in pharmaceutical studies by including both eyes of qualified and consenting patients. This has not been a widely accepted research practice in the past, due to the impression that fellow eyes are not independent and might introduce bias into studies. Our preliminary data, reported here, suggest that fellow eyes may well be independent in terms of therapeutic responses to IOP-lowering medications, and the benefits of halving study sample sizes may well outweigh the probably small risk of bias. Prospective confirmation of these findings is necessary, and could be easily accomplished by post hoc analysis of data collected during studies such as the Ocular Hypertension Treatment Study. In that study, patients randomized to the treatment arm underwent unioocular trials during the initiation of treatment. From that large database, further information about the value of the monocular trial and the fellow-eye response could be obtained.

References

1. Shields MB. Textbook of Glaucoma. 4th ed. Baltimore: Williams & Wilkins; 1998:378.
2. Stamper RL, Lieberman MF, Drake MV. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. 7th ed. St. Louis: Mosby; 1999:424.
3. Ritch R, Shields MB, Krupin T. Chronic open-angle glaucoma: treatment overview. In: Ritch R, Shields MB, Krupin T, eds. The Glaucomas. 2nd ed. St. Louis: Mosby; 1996:1512.
4. Piltz J, Gross R, Shin DH, et al. Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the Ocular Hypertension Treatment Study. Am J Ophthalmol 2000; 130:441–53.
5. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. Ophthalmology 1995;102:1743–52.
6. Katavisto M. The diurnal variations of ocular tension in glaucoma. Acta Ophthalmol (Copenh) 1964;78:1–130.
7. Wilensky JT, Gieser DK, Dietsche ML, et al. Individual variability in the diurnal intraocular pressure curve. Ophthalmology 1993;100:940–4.
8. Realini T, Barber L, Burton D. Frequency of asymmetric intraocular pressure fluctuations among patients with and without glaucoma. Ophthalmology 2002;109:1367–71.
9. Zimmerman TJ, Kaufman HE. Timolol. A beta-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol 1977;95:601–4.